New Approaches to Stability Testing

PQRI Stability Shelf Life Working Group

Brief History of the Working Group

- PQRI STABILITY SHELF LIFE WG (SSL)
  - proposal approved August 2006
  - WG established late 2006
    - first meeting November 2006
    - members include statistical and pharmaceutical scientists from industry, academia and FDA
    - contacts with other stability working groups
  - workplan approved May 2007
  - next face-to-face meeting scheduled for Spring 2009

Brief History of the Working Group

- Objectives
  - propose best practices for estimating shelf life with respect to stability quality attributes
  - develop statistical methods for estimating shelf life which are consistent with common understanding of shelf life
  - demonstrate methods for estimating shelf life to provide a more accurate estimate
  - propose estimation methods to allow sponsor to define own risk and risk management practices

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Understanding Shelf Life

- Patient Expectation
  - true shelf life for a particular batch is the longest time that all “dosage units administered” are safe and efficacious
    - implied expectation when patient receives dosage
  - unrealistic expectation
    - cannot assure efficacy of 100% of product
    - not possible to prove by testing

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Understanding Shelf Life

- ICH Q1E
  - The statistically estimated shelf life is the last time point that the mean of all “dosage units” in a batch remain within the acceptance criteria at a confidence level of 95%.
  - A shelf life is then “extrapolated” using a decision tree based on product performance at accelerated or intermediate conditions. If the “extrapolated” shelf life is less than or equal to the estimated shelf life, it then becomes the proposed shelf life.
    - by-batch philosophy
    - does not account for batch-to-batch variability

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Understanding Shelf Life

- ICH Q1A(R2)
  - The purpose of a stability study is to establish, based on a minimum of 3 batches of drug product, a shelf life….applicable to all future batches of the drug product manufactured and packaged under similar circumstances.
  - true shelf life is the longest time such that the probability to comply with requirements is certain
    - certainty equates to a probability of 1.0
    - impossible to achieve
    - currently methodology often penalizes applicant for data sets comprised of more than 3 batches

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Understanding Shelf Life

- SSL WG Working Definition
  - true shelf life is the longest time such that the proportion of “tablets” complying with requirements is at least q
  - q defined by sponsor in agreement with regulatory
    - defines acceptable risk taken on by sponsor
    - accommodates shelf life based on either mean batch response or individual “tablet"
  - addresses both between and within batch variation
  - extends inference of shelf life to future batches

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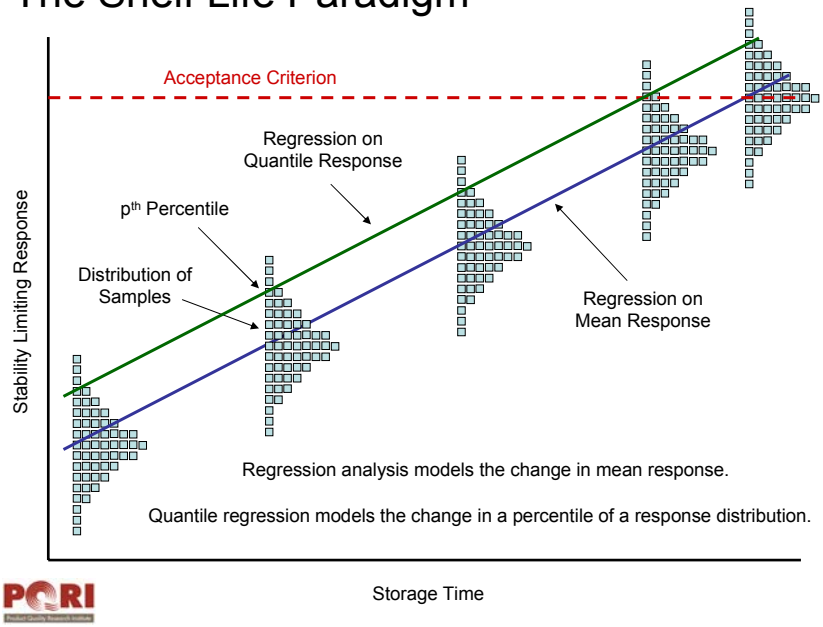
The Shelf Life Paradigm



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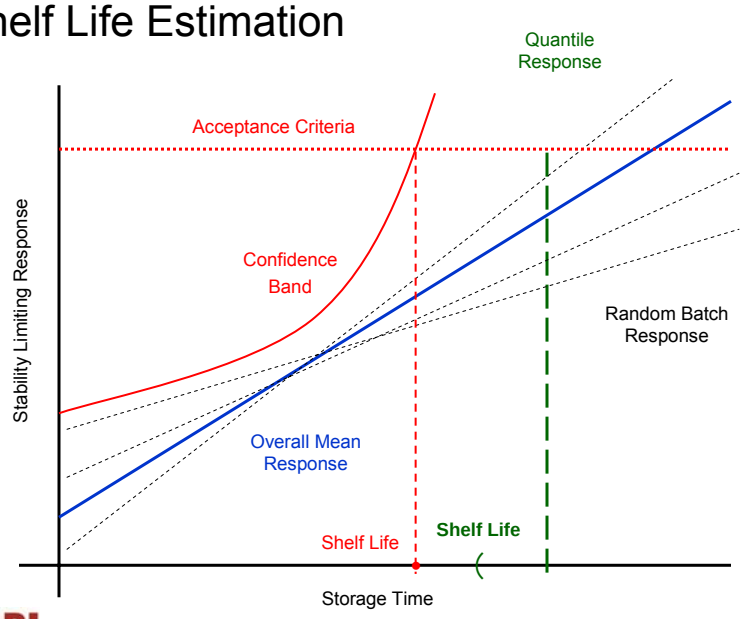
Shelf Life Estimation



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Simulated Data Example

The following example is based on the results of a 12-month stability trial for a pharmaceutical product.

- Assay was one stability limiting characteristics
- acceptance criteria: 95% to 105%
- simple linear (straight line) response model
- three batches included in study
- 24-month shelf life was desired

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Simulated Data Example

Using current ICH statistical methodology, the batch data could not be pooled (p=0.0314 testing directly to common model).

The results of not being able to pool the batch data is to use the most limiting (worst case) batch results to estimate shelf life.

- based on confidence bounds about each batch's mean response
- batch with most rapid decline provides shortest shelf life (worst case)
- gave estimated shelf life of about 22 months

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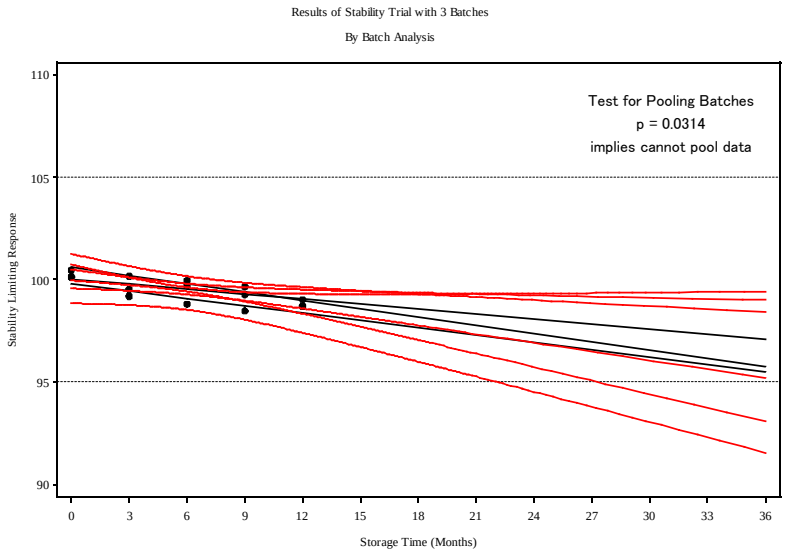
Shelf Life Estimation using ICH



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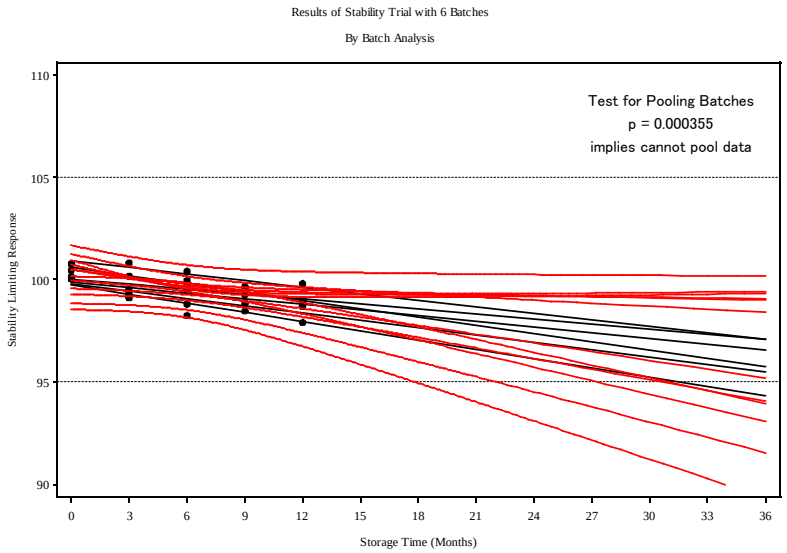
Simulated Data Example

In an attempt to achieve the desired 24-month shelf life claim, three more batches were added to the stability analysis.

Shelf Life Estimation using ICH



Simulated Data Example

Using WG proposed methodology,

- modeling overall mean response
- accommodating both between and within batch variation
- based on confidence bounds about overall mean batch response
- using reflection method (not most optimal, but easiest for today) to calibrate shelf life estimate
- batch with most rapid decline (worst case) provides a better understanding of batch-to-batch variation
- gave estimated shelf life of about 35 months

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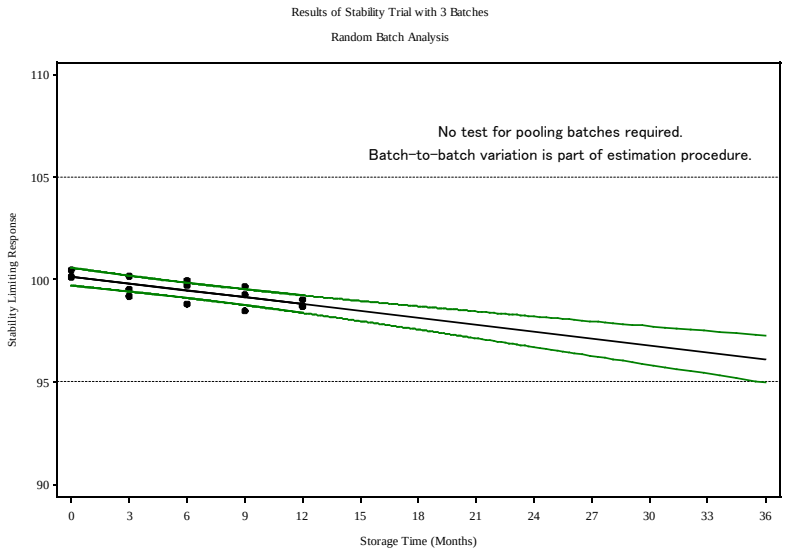
Random Batch Analysis



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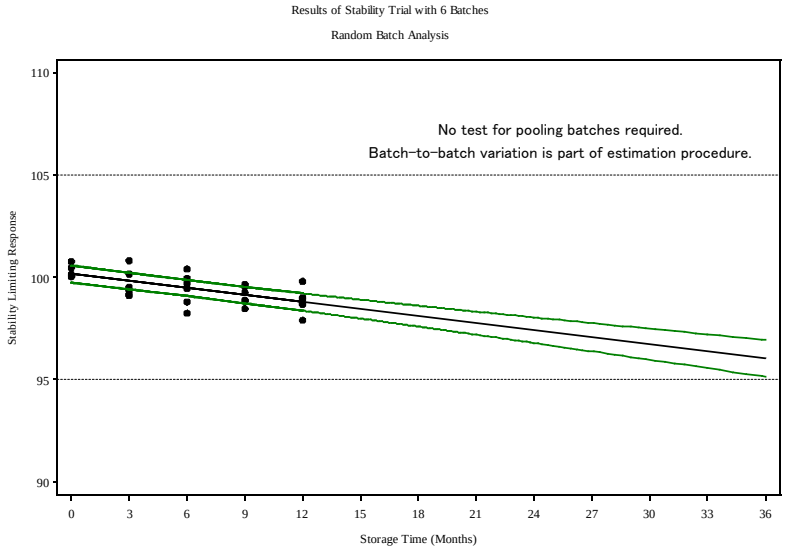
Random Batch Analysis



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Summary

Proposed estimation methodology provides a consistent and flexible methodology for directly estimating shelf life

- allows estimation on mean or percentile response
- sponsor defines “quality” through managing of risk
- provides more information about stability process
- consistent with how acceptance criteria is defined
- uses between and within batch variation
- extends inference to future batches
- does not penalize for additional data

The Working Groups efforts continue with a methodology to be proposed at the end of the year.

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PQRI Stability Shelf Life Working Group

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